expectancy [11], it is important to acknowledge all benefits and harms of the treatment, not only mortality. When treating hypertension in people with dementia, for example, our review showed that in addition to cerebro- and cardiovascular events and mortality, a range of potential outcomes should be taken into account such as progression of the disease, falls, depression, hypotension, polypharmacy and interaction with cholinesterase inhibitors [12]. A similar range of outcomes might be relevant for older people with frailty. To provide evidence-based, individually tailored healthcare, large studies are needed to look at multiple outcomes simultaneously with enough statistical power to investigate these and their interactions, instead of focusing on one primary outcome.

Key points

• When making decisions regarding antihypertensive treatment, the functional and cognitive statuses of the patient should be taken into account.
• Frequent blood pressure monitoring is required for people with frailty.

References

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Is frailty in the elderly linked to inflammation?

With an increase in life expectancy around the world, the period of life spent in dependency towards the later part of life has increased and is now a subject of great importance. This has a significant effect on quality of life in the later years. There have been a number of studies to investigate the causes of frailty in later years. A number of these have linked quality of life in later years to genetic factors. For example, a study of 349 elderly women found that there was a strong association with several single-nucleotide polymorphisms (SNPs) in genes encoding apoptotic and transcription regulation factors [1]. The role of inflammation in the pathogenesis of frailty in particular has also long been hypothesised [2].

The study by Mekli et al. shows a significant association between frailty and a SNP in the first intron of the interleukin (IL)-18 gene and a less significant one with that for the IL-12 gene. IL-18 is an inflammatory cytokine of the IL-1
superfamily, also termed IL-1-family member 4 (IL1F4). It was originally discovered as an inducer of interferon-γ [3], a property shared with IL-2. Like IL-1-α and IL-1-β, IL-18 is produced by macrophages and acts as a pro-inflammatory cytokine. This SNP (rs360722) was also found to be associated with susceptibility to rheumatoid arthritis [4] and with the inflammatory response associated with cardiopulmonary bypass surgery [5], but had not been identified as a possible causal variant in the previously cited study on frailty [1].

This finding builds on previous evidence supporting the hypothesis that there is an association between inflammation, frailty and in a broader context ageing. Inflammation has previously been linked with loss of muscle mass in other conditions; in the 1980s, it was found that plasma from patients with trauma or sepsis contain elevated levels of a soluble factor that induces muscle proteolysis [6], which is thought to be related to IL-1 [7]. With regards to ageing, age-related conditions, including frailty, are associated with increased production of inflammatory cytokines [8]. A population study on over 4,700 subjects identified a correlation between frailty and high levels of the inflammatory marker C-reactive protein [9]. However, levels of biomarkers of inflammation can change depending on a number of conditions so that other co-morbidities may act as confounding factors when trying to relate inflammation with frailty. Furthermore, a recent meta-analysis of Genome-Wide Association Studies (GWAS) into age-associated disease has found an association with SNPs in a number of inflammatory and cell senescence pathways and ageing [10].

The finding might potentially help identifying, with a simple genetic test, patients at risk of becoming frail. This finding could be important for instance in patients’ stratification if anti-inflammatory therapies were to be tested in clinical trials to identify patients who may benefit from treatments and those where other factors have more weight in contributing to frailty.

What the present study is not telling us is whether this polymorphism is associated with higher IL-18 levels, either under normal conditions or in any age-related disorders that may occur along with frailty. Measurement of IL-18, as well as of other cytokines of the IL-1 family, can be easily carried out in serum with commercially available kits. Future studies will need to confirm in larger cohorts of subjects whether this SNP variation is associated with differences in IL-18 levels.

This may be another valuable piece of information that will favour the role of inflammation as a component in the development of frailty. If is proved, it will be useful in developing therapeutic targets for the management of frailty and possibly even consider it being reversed. A study of this genetic predisposition will help to target the population which may benefit most from specific therapies.

**Key points**

- Significant associations have been demonstrated between frailty and SNPs in genes that regulate production of inflammatory cytokines (IL-18 and IL-12).
- These findings support the hypothesis that there is an association between inflammation, frailty and in a broader context ageing.
- A simple genetic test might identify subjects at high risk of becoming frail due to activated inflammation—such subjects are ideal candidates for testing of anti-inflammatory therapies to prevent or delay onset of frailty.

**Conflicts of interest**

None declared.

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**References**